

Error Thresholds on Dynamic Fitness-Landscapes

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In this paper we investigate error-thresholds on dynamics fitness-landscapes. We show that there exists both lower and an upper threshold, representing limits to the copying fidelity of simple replicators. The lower bound can be expressed as a correction term to the error-threshold present on a static landscape. The upper error-threshold is a new limit that only exists on dynamic fitness-landscapes. We also show that for long genomes on highly dynamic fitness-landscapes there exists a lower bound on the selection pressure needed to enable effective selection of genomes with superior fitness independent of mutation rates, i.e., there are distinct limits to the evolutionary parameters in dynamic environments.

Ever since Eigen's work on replicating molecules in 1971 [1], the concept of quasi-species has proven to be a very fruitful way of modeling the fundamental behavior of evolution. A quasi-species is an equilibrium distribution of closely related gene sequences, localized around one or a few sequences with high fitness. The combination of simplicity and mathematical preciseness makes it possible to isolate the effects of different fundamental parameters in the model. It also makes it possible to capture some general phenomena in nature, such as the critical relation between mutation rate and information transmission [1,2]. The kinetics of these simple systems has been studied in great detail as the formulation has allowed many of the techniques of statistical physics to be applied to replicator and evolutionary systems. See for instance [1–15].

The appearance in these models of an error-threshold (or error-catastrophe) as an upper bound on the mutation rate, above which no effective selection can occur, has important implications for biological systems. In particular it places limits on the maintainable amounts of genetic information [1,2,16] which puts strong restrictions on possible theories for the origins of life. It is interesting to note that some RNA-viruses seem to have evolved mutation rates that are close to the error-threshold [2] [16].

Studies of quasi-species until now have focused on static fitness-landscapes. Many organisms in nature however live in a quickly changing environment [17]. This is especially important for viruses and other microbial pathogens that must survive in a host with an highly dynamic immune system for which there only exist tight and temporary niches with high fitness (for the pathogen).

In this paper we investigate how the critical mutation rate of the error threshold is affected by a dynamical fitness-landscape. We show how the critical mutation

rate is lowered by shifts of the fitness-peak. A simple analytical expression for this critical copying fidelity is also presented. It also turns out that if the selection pressure is too small, the fitness-landscape moves too fast and the fitness encoding genome is too large, the population will lose the fitness-peak independent of mutation rate. This shows the existence of regions in parameter space where no selection can occur despite possibilities of adjusting copying-fidelity.

In brief a quasi-species consists of a population of self-replicating genomes represented by a sequence of bases s_k , $(s_1 s_2 \dots s_n)$. Hereafter we will assume binary bases $\{1, 0\}$ and that all sequences have equal length n though these restrictions are easily relaxed. Every genome is then given by a binary string $(011001\dots)$, which can be represented by an integer k ($0 \leq k < 2^n$).

To describe how mutations affect a population we define W_k^l as the probability that replication of genome l gives genome k as offspring. For perfect copying accuracy, W_k^l equals the identity matrix. Mutations however give rise to off diagonal elements in W_k^l . Since the genome length is fixed to n we will only consider point mutations, which conserve the genome length.

We assume that the point mutation rate $p = 1 - q$ (where q is the copying accuracy per base) is constant in time and independent of position in the genome. We can then write an explicit expression for W_k^l in terms of the copying fidelity:

$$W_k^l = p^{h_{kl}} q^{n-h_{kl}} = q^n \left(\frac{1-q}{q} \right)^{h_{kl}} \quad (1)$$

where h_{kl} is the Hamming distance between genomes k and l , and n is the genome length. The Hamming distance h_{kl} is defined as the number of positions where genomes k and l differ.

The equations describing the dynamics of the population now take a relatively simple form. Let x_k denote

the relative concentration and A_k the fitness of genome k . We then obtain the rate equations:

$$\dot{x}_k = \sum_l W_k^l A_l x_l - e x_k \quad (2)$$

where $e = \sum_l A_l x_l$ and the dot denotes a time derivative. The second term ensures the total normalization of the population (as $\sum_l x_l = 1$) so that x_k describes relative concentrations.

To create a dynamic landscape we consider a single peaked fitness landscape [2] whose peak moves, resulting in different optimal gene sequences at different times. Formally we can write $A_{k(t)} = \sigma$ and $A_l = 1 \forall l \neq k(t)$ where the (changing) genome $k(t)$ describes how the peak moves through sequence space. If $k(t)$ is constant in time the rate equation [Eq. 2] corresponds to the classical (static) theory of quasi-species studied by Eigen and others.

We allow the peak in the fitness landscape to move to one of its closest neighbors (chosen randomly). In this paper we assume that movements occur with a fixed frequency but one could also consider a probabilistic movement.

The mutation matrix W describes point mutations which occur with equal probability independent of position in the genome. This imposes a symmetry on the rate equations, dividing the relative concentrations into error classes Γ_i described by their Hamming distance i from the master sequence (Γ_0). This reduces the effective dimension of the sequence space from 2^n to $n + 1$ thereby making the problem analytically tractable. The use of asymmetric evolution operators (such as recombination) or fitness landscapes is obviously significantly more problematic and is the subject of ongoing work. When the fitness peak moves this landscape symmetry will be broken since one sequence in Γ_1 will be singled out as the new master sequence. This would only affect the results we present below if the mean time between shifts in the fitness-landscape was small — as there would then be a substantial concentration of the old master sequence present when the peak moves back into this error-class. We assume the dynamics to be slow enough for this not to be a problem.

Moving the fitness peak then corresponds to applying the following co-ordinate transformation to the concentration vector:

$$R = \begin{pmatrix} 0 & \frac{1}{n} & 0 & \dots \\ 1 & 0 & \frac{2}{n} & \dots \\ 0 & \frac{n-1}{n} & 0 & \dots \\ \vdots & \vdots & \vdots & \ddots \end{pmatrix} \quad (3)$$

To study the population dynamics we may divide the dynamics into cycles from time 0 to τ , where τ is a parameter determining the number of generations between shifts of the fitness peak when the evolution proceeds as for a static landscape. We then apply the R transformation

to the concentration vector. The resulting concentration distribution is used as the initial condition for the rate equations from time τ to 2τ and so on. These population dynamics [Eq. 2 and R] may be solved numerically as shown in Fig. 1 (after the initial transient) where $\tau = 5$, $\sigma = 10$, $q = 0.999$ and string-length $n = 50$.

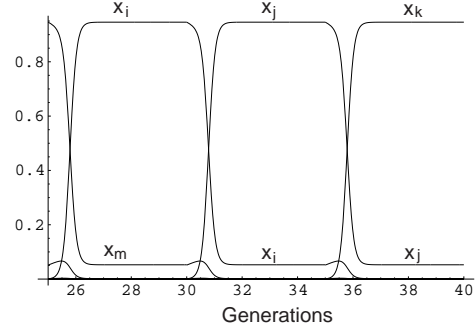


FIG. 1. This plot shows the population dynamics for gene sequences of length 50 when the fitness peak moves every fifth generation ($\tau = 5$) and the height of the fitness peak σ is 10. The result is shown from $t = 25$ to remove initial transients.

A simple approximation of the model presented above enables us to derive analytical expressions for the error-thresholds on a dynamic fitness-landscape. Neglecting back mutations into the master-sequence, we can write the rate equation for the master-sequence on a static fitness-landscape as

$$\dot{x}_{mas} = Q \sigma x_{mas} - e x_{mas} \quad (4)$$

where $Q = q^n$ is the copying fidelity of the whole genome and $e = \sigma x_{mas} + 1 - x_{mas}$. The asymptotic concentration of master-sequences is

$$x_{mas}(t) \rightarrow \frac{Q\sigma - 1}{\sigma - 1} \text{ when } t \rightarrow \infty \quad (5)$$

This implies that the error-threshold on a static fitness-landscape occurs when

$$Q^{stat} = \frac{1}{\sigma} \quad (6)$$

(see e.g., [1,2]). This result is also intuitively clear since the superior fitness (and hence growth rate) of the master-sequence must compensate for the loss of Γ_0 individuals due to mutations that occur during replication.

The intuitive picture of the error-threshold on a dynamic fitness-landscape is different: what determines the critical mutation rate is whether the master-sequence will have time to regrow between the shifts of the fitness-peak. To find an analytical approximation for the error-threshold we have to expand Eq. (4) to include the dynamics of error-class one as well as the master-sequence. This is necessary since the fitness-peak moves into error-class one every τ time-steps. We can, however, make a large simplification by assuming the growth of the master-sequence to be in the exponential regime, i.e., that we can

neglect the non-linearity in Eq. (4). This is a good approximation near the error-threshold as, for these values of q , the master-sequence will not have time to approach any kind of equilibrium before the peak shifts again. We can thus write an approximation of the rate equations for the master-sequence and a representative member of error-class one:

$$\begin{aligned}\dot{x}_{mas} &= (Q\sigma - 1)x_{mas} \\ \dot{x}_{1j} &= \tilde{Q}\sigma x_{mas} + (Q - 1)x_{1j}\end{aligned}\quad (7)$$

where mutations into the member of error-class one are neglected and $\tilde{Q} = (1 - q)q^{n-1}$ describes mutation from x_{mas} into x_{1j} . We now assume $x_{1j}(0) = 0$, which is a good approximation since x_{1j} is (almost always) in Γ_2 before the shift. The solutions to Eq. (7) using this boundary condition can be written as

$$\begin{aligned}x_{mas}(t) &= x_{mas}(0)e^{(q^n\sigma-1)t} \\ x_{1i}(t) &= x_{mas}(0)\left(\frac{(e^{(q^n\sigma-1)t} - e^{(q^n-1)t})(1-q)\sigma}{(\sigma-1)q}\right)\end{aligned}\quad (8)$$

The shifting involves the move of the fitness peak to one of the sequences in error-class one at time $t = \tau$. The initial concentration of master-sequences at the beginning of a shift cycle is therefore $x_{mas}(0) = x_1(\tau)$. If the concentration of the master-sequence after the shift is lower than immediately after the previous shift, i.e. $x_{mas}(0) > x_1(\tau)$, the distribution of concentrations will converge towards a uniform distribution. This is, in effect, a definition of the error-threshold. A condition for effective selection is then given by inserting $x_{mas}(0) < x_1(\tau)$ into Eq. (8). We then derive a master-sequence growth parameter

$$\kappa \equiv \frac{(e^{(q^n\sigma-1)\tau} - e^{(q^n-1)\tau})(1-q)\sigma}{(\sigma-1)q} > 1 \quad (9)$$

It is not possible to find exact analytical solutions for the roots of Eq. (9) and hence the error-thresholds. Fig. 2 shows the region where Eq. (9) can be expected to hold. The figure also shows the existence of two error-thresholds, q_{lo}^{dyn} and q_{hi}^{dyn} corresponding to the real roots of $\kappa = 1$. The lower threshold is a new version of the static error-threshold, with a perturbation resulting from the movement of the fitness-landscape. The upper threshold is a new phenomenon that appears only on dynamic fitness-landscapes. Its existence is intuitively clear — if the mutation rate is very close to zero, there will not be enough individuals present on the new peak position when the shift occurs to maintain a steady occupancy of the master sequence, i.e. the peak moves out from under the quasi-species and the population will not be able to track shifts in the fitness-landscape.

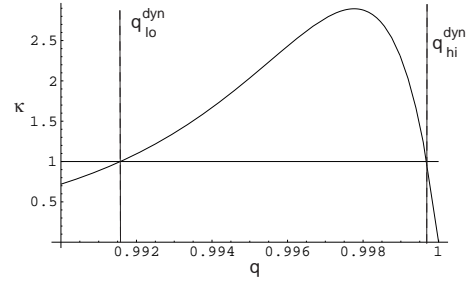


FIG. 2. The left hand side of Eq. 9 is plotted as a function of the copying fidelity q . The genome length $n = 50$, $\tau = 2$ and $\sigma = 5$. The lower threshold is located at $q_{lo}^{dyn} = 0.988$ and the upper threshold at $q_{hi}^{dyn} = 0.9997$.

Analytical approximations to the error-thresholds can be found by assuming different dominant terms in the two different regions. To find the lower threshold q_{lo}^{dyn} we assume q^n to dominate the behavior. Solving for q^n gives

$$q^n \approx \frac{\tau - \ln\left(\frac{\sigma}{\sigma-1} \cdot \frac{1-q}{q}\right)}{\sigma\tau} \quad (10)$$

We can use Eq. (10) to find a first order correction in τ to the static threshold by putting $q = \frac{1}{\sigma^{1/n}}$ on the right hand side

$$Q_{lo}^{dyn} \approx \frac{1}{\sigma} - \frac{\ln(\sigma^{1/n} - 1)}{\tau\sigma} \quad (11)$$

where we also made the approximation $\frac{\sigma}{\sigma-1} \approx 1$. This is an expression for the lower error-threshold on a dynamic fitness-landscape. Note that $Q_{lo}^{dyn} \rightarrow Q_{crit}$ when $\tau \rightarrow \infty$, i.e. we recover the stationary landscape limit.

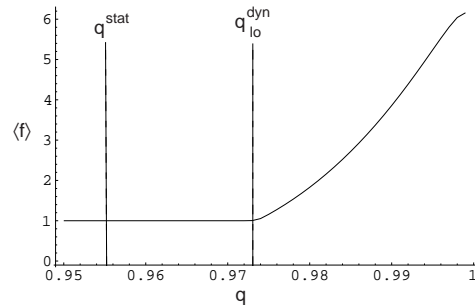


FIG. 3. The mean fitness is plotted as a function of the copying fidelity per base q . The fitness peak moves every other generation ($\tau = 2$), the string-length n is 50 and the growth superiority of the master sequence σ is 10. The error-threshold occurs at the predicted value $q_{lo}^{dyn} = 0.973$. The static error-threshold is located at $q^{stat} = 0.955$.

Fig. 3 shows the mean fitness of a population as a function of the copying-fidelity. When q is below q_{lo}^{dyn} , the concentration of master-sequences is approximately zero and the mean fitness will therefore be 1. The figure is

based on numerical simulations of the full rate equations [Eq. 2]. Note that the predicted value of q_{lo}^{dyn} given by Eq. (11) is quite accurate. Further comparisons to numerical solutions to the full dynamics are shown in table I.

Both the qualitative and quantitative dynamics of both error thresholds have been verified by computer simulations using large populations to approximate the deterministic dynamics.

The critical copying fidelity Q_{lo}^{dyn} depends on the genome-length. This is not surprising since the fitness-peak shifts into a specific member of Γ_1 , which consists of n different gene-sequences. It is, however, a direct consequence of the dynamic fitness-landscape since the static error-threshold is independent of genome-length. This effect is demonstrated in Fig. 4, where Q_{lo}^{dyn} versus the genome-length is plotted. The perturbation from the static error-threshold increases with genome-length. The derivative is however decreasing and for reasonable values of $\tau \gg 1$ and $\sigma \gg 1$ the static and dynamic error-threshold are of the same order of magnitude and show the same scaling behaviour.

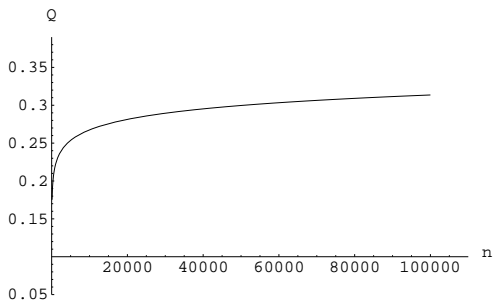


FIG. 4. The plot shows how the error-threshold Q_{lo}^{dyn} given by Eq. (11) depends on the genome-length. The parameters describing the fitness-landscape are fixed, $\sigma = 10$ and $\tau = 5$. The static error-threshold is located co-incident with the x-axis at $Q^{stat} = 0.1$.

τ	σ	n	$q_{threshold}$	q_{lo}^{dyn}	q^{stat}
2	10	25	0.940	0.941	0.912
2	10	50	0.973	0.973	0.955
2	5	50	0.988	0.988	0.968
5	10	50	0.963	0.964	0.955

TABLE I. The table shows results of numerical solutions of the error-threshold compared to predicted values given by Eq. (11) and the threshold for the corresponding static fitness-landscape.

An analytical approximation to the new upper threshold can be found by assuming q to be very close to 1 and therefore the $(1 - q)$ -term dominates the behaviour of Eq. (9). Again assuming $\sigma \gg 1$ and putting $q^n = 1$, gives

$$q_{hi}^{dyn} \approx 1 - e^{-(\sigma-1)\tau} \quad (12)$$

Explicit numerical solutions of the full dynamics confirm that this threshold exists and is predicted by Eq. (12). For most values of σ and τ , q_{hi}^{dyn} is very close to 1 (e.g. $(\sigma - 1)\tau = 50$ gives 10^{-22} as a lower bound on the mutation rate per base pair). Finite population affects are however significant for the upper error-threshold. In real biological populations this may be important. More detailed studies of these issues are under preparation.

It is important to note that q_{hi}^{dyn} is independent of the genome-length. The total copying fidelity $Q_{hi}^{dyn} = \left(q_{hi}^{dyn}\right)^n$ will then depend strongly on the genome-length. This means that as the genome-length increases, the evolvable gap in between the two error-thresholds narrows.

On a static fitness-landscape it is always possible to find copying fidelities high enough for evolution to be effective. It turns out that this is no longer the case for dynamic fitness-landscapes. There exist regions in parameter-space (spanned by σ , τ and n) where solutions to Eq. (9) cease to exist. This happens when the upper and lower error-thresholds coincide or, to put it differently, when the maximum (taken over q) of the left hand side of Eq. (9) become less than 1. To find this convergence point it is better to search for a direct approximation of q that maximizes the left hand side of Eq. (9) as the approximations for upper and lower error-thresholds given above become less accurate when they are close together. To do this we assume the leading behaviour is determined by the factor $e^{(q^n \sigma - 1)\tau} (1 - q)$. Taking the derivative of this expression and setting it to zero gives the equation $q^{n-1} (1 - q) = \frac{1}{n\sigma\tau}$. Assuming q to be very close to 1, and hence $q^{n-1} \approx 1$ gives

$\tau \setminus n$	50	500	5000	50000	10^9
1	7.8	10.4	13.0	15.5	25.9
10	1.7	2.0	2.2	2.4	3.5
50	1.1	1.2	1.2	1.3	1.5

TABLE II. The minimum selection pressure required for an infinite population to track the peak is listed for different values of the genome length n and the number of generations between shifts of the fitness-peak τ .

$$q_{max} \approx 1 - \frac{1}{\sigma\tau n} \quad (13)$$

This approximation for q_{max} can be substituted into Eq. (9). It is easy find points in phase space where this inequality starts to hold by fixing two parameters (e.g., τ and n) and then numerically solving for the third (σ). Table II shows the minimal height of the fitness-peak for different values of τ and n . The required selective pressure becomes large for fast moving fitness-landscapes and large genome lengths.

In conclusion we have shown existence of, and derived analytic expressions for, two error-thresholds on a simple dynamic fitness-landscape. The lower threshold is a perturbation of the well known error-catastrophy that exists a static fitness-landscape that accounts for the destabilizing effect of the changing environment. The existence of an upper bound on the copying fidelity is a new phenomenon, only existing in dynamic environments. The presence of this upper bound results in the existence of critical regions of the landscape parameters (σ , τ and n) where the two thresholds coincide (or cross) and therefore no effective selection can occur. Thus dynamics landscapes have strong constraints on evolvability.

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